II. Brief non-technical description of the proposed experiment.

TIL (tumor infiltrating lymphocytes) therapy is a new experimental treatment for some patients who have advanced cancer. A portion of the tumor is removed, grown in the laboratory under conditions which allow the cancer cells to die, but the invading immune cells (called lymphocytes) to multiply. These TIL are then grown in the laboratory to very large numbers. The TIL which are presumed to be the patient's own cancer fighting cells, are infused into a vein of the patient. The TIL are thought to circulate through the body, find the areas of cancer, and then invade and kill the cancer cells.

This TIL therapy has resulted in a substantial decrease in tumor size in about 40% of patients with melanoma treated thus far. The tumor regressions due to this treatment have lasted for varying times from a few months to approximately one year. We have also demonstrated that these TIL accumulate in tumor deposits after the TIL are injected intravenously. We have been working to improve the TIL treatment and have developed evidence to suggest that TIL that are capable of secreting a substance with antitumor activity (called tumor necrosis factor or TNF) might have increased therapeutic antitumor activity. We have thus developed methods for introducing genes into TIL that can increase their production of TNF.

The method that we use for introducing this gene is called retroviral mediated gene therapy. In this technique, new genes are inserted into the cells using a virus which has been modified so that it can introduce a gene into a cell but the virus itself cannot divide and survive. The cells with the new gene then produce approximately 10-100 times more TNF than the TILs without the introduced gene.

It is not known whether these gene transduced TIL will have a higher anti-tumor activity than normal TIL, although this is a questions that will be, in

part, addressed in this clinical protocol. Because there are possible added side effects resulting from the increased production of TNF by TIL the clinical protocol involves the use of increasing the numbers of cells starting at a very low cell number that is not expected to cause side effects. If levels of the transferred cells given to patients do cause side effects then no higher doses will be given. The gene modified TIL will be administered along with another substance called interleukin-2 which helps keep these cells alive in the body.

Extensive studies will be performed in patients to monitor the survival of the TIL in the patient as well as to determine any possible side effects or therapeutic benefit that result from this treatment.